REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1, 12, 22, 34, and 45 have been amended without prejudice. Support for the amendments to claims 1, 12, and 22 can be found, e.g., in paragraph [0093] of the specification as filed. Support for the amendments to claim 45 can be found, e.g., in paragraph [0014] of the specification as filed.

Claims 52-68 have been previously canceled without prejudice in response to the Restriction Requirement.

Claims 1-51 and 69-73 are pending. It is respectfully submitted that no new matter has been added by virtue of this amendment.

II. Double Patenting

In the Office Action, claims 1-51 and 69-73 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9, 14-16, 98-100, and 125-126 of U.S. Application No. 10/413,022 in view of U.S. Patent No. 5,476,093 and Noakes (Journal of Aerosol Medicine, 1995 Spring; 8 Suppl. 1:S3-7).

In response, Applicants respectfully submit that the filing of a terminal disclaimer will be considered upon notification that the pending claims are otherwise allowable.

III. Claim Rejections- 35 U.S.C. § 103

Claims 1-51 and 69-73 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 2002/0006933 to Gupta et al. ("the Gupta publication) in view of U.S. Patent No. 5,699,789 to Hendricks ("the Hendricks patent"); Ensuring Patient Care, 2nd ed., 1999, pages 15-21; U.S. Patent No. 5,476,093 to Lankinen ("the Lankinen patent"); Lucas et al., (Pharmaceutical Research, 1999; 16(10):1643-1647); and Noakes (Journal of Aerosol Medicine, 1995 Spring; 8 Suppl. 1:S3-7."

In response, Applicants submit that that the combination of documents cited by the Examiner does not teach or suggest each and every element of the present claims for the reasons set forth below.

Applicants submit that the Examiner has acknowledged that US 2002/0006933 does not describe the human inhalation doses of apomorphine recited in amended claims 1 and 34. Applicants further submit that US 2002/0006933 teaches a dose range of 0.5-2.0 mg apomorphine for its purported 'inhalation' in dogs (Example 2).

The Examiner's attention is directed to paragraph [0074] of US 2002/0006933 where it is stated that "[a]n 8 mg human dose compares well with about 1.33 mg apomorphine dose in dogs." Accordingly, Applicants submit that the inhaled dose range described in US 2002/0006933 is equivalent to a 3-12 mg human dose range.

In contrast, the maximum human inhalation dose recited in amended claims 1 and 34 is 1.6 mg.

Applicants submit that there is no suggestion in US 2002/0006933 that doses of 1.6 mg or less, as employed in the methods of amended claims 1 and 34, would be therapeutically effective in humans. In fact, paragraph [0074] of US 2002/0006933 clearly advocates using doses of at least 0.5 mg in dogs (equivalent to 3 mg in humans), whether administered by inhalation, intranasally or orally, so as to achieve plasma drug levels comparable to or higher than those achieved with 2 mg sublingual tablets in dogs without the comparable side effects. Therefore, Applicants submit that US 2002/0006933 actually teaches away from using doses "from about 100 to about 1600 micrograms of apomorphine or a pharmaceutically acceptable salt or ester thereof" as recited in amended claims 1 and 34.

In the event the Examiner asserts that the dosage conversion described in paragraph [0074] does not apply to administration by inhalation, Applicants submit that, in that situation, US 2002/0006933 fails to provide the skilled person with *any* guidance on specific human inhalation doses of apomorphine, and, therefore, does not teach or suggest the specific human inhalation doses recited in amended claims 1 and 34.

With regard to the Examiner's statement that "optimization of dosage range to herein claimed in order to achieve the optimal therapeutic plasma level of apomorphine is obvious as being within the skill of the artisan" because "according to '933, the therapeutic plasma concentration of apomorphine as about 5-10 ng/ml," Applicants submit that the therapeutic plasma concentration of apomorphine was not investigated in this document; rather, it focuses on the avoidance of side effects normally associated with apomorphine therapy. Accordingly, the skilled person learns little about the plasma level of apomorphine that should be attained for a therapeutic effect in humans to be observed from the disclosure of US 2002/0006933. Applicants respectfully submit that the mere recitation of the blood plasma level of apomorphine in dogs is insufficient to establish a prima facie case of obviousness of the specific human inhalation doses recited in the amended claims, for example, because US 2002/0006933 does not provide motivation for the skilled person to select the specific doses recited in the methods of the amended claims.

Applicants submit that, contrary to the teaching in US 2002/0006933, the methods claimed in amended claims 1 and 34 recite a dose "of from about 100 to about 1600 micrograms of apomorphine or a pharmaceutically acceptable salt or ester thereof". The Applicants have discovered that such doses are, in fact, therapeutically effective, and that a response to apomorphine may be observed rapidly after inhalation. See e.g., paragraph [0093] of the present specification.

With regard to the Examiner's statement that " '933 also teaches the employment of adjunct agents such as lactose," Applicants respectfully note that the use of lactose in the

formulations of US 2002/0006933 is only described in connection with solid dosage forms for oral administration (paragraphs 55 and 56). Accordingly, Applicants submit that US 2002/0006933 does not teach or suggest using lactose as a carrier in an inhalation composition as recited in claim 24.

Applicants further submit that, even if the skilled person did consider preparing an inhalable formulation comprising lactose (a position which is refuted), the inclusion of the high doses of apomorphine that are taught in US 2002/0006933 would require large amounts of powder to be administered to the lung. Applicants note that the skilled person would be aware, e.g., that the administration of large powder volumes to the lung is, however, uncomfortable or even dangerous. Therefore, Applicants submit that the the skilled person reading US 2002/0006933 would clearly not be prompted to reformulate the solid dosage form formulations described in US 2002/0006933 as inhalable formulations comprising lactose, e.g., because the resultant formulations would have totally undesirable properties.

For the foregoing reasons, Applicants submit that the methods recited in amended claims 1 and 34 are not taught or suggested by US 2002/0006933, either alone, for the reasons discussed above, or in combination with the cited documents, for the reasons discussed below.

Applicants submit that it is improper to combine US 2002/0006933 with US 5,699,789, Ensuring Patient Care, US 5,476,093, Lucas P. *et al.* and Noakes T.J, which are purportedly directed to the field of inhalation therapy, for the following reasons.

Applicants submit that US 2002/0006933 teaches away from the field of inhalation therapy and toward intranasal or oral therapy instead (see the Detailed Description, in particular paragraphs [0048]-[0062]). Indeed, as the Examples show, the incidence of emesis (a known side effect of apomorphine administration, and a side effect that the inventors named in US 2002/0006933 were trying to avoid) was greatly reduced when the drug was administered intranasally (see Table 1) or orally (see Table 5), compared to when it was administered by

'inhalation' (see Table 3). Furthermore, the bioavailability of apomorphine was far greater when apomorphine was administered intranasally than when it was administered by 'inhalation' (see Tables 2 and 4). Thus, Applicants submit that a person skilled in the art concerned with the administration of apomorphine for the treatment of sexual dysfunction would not have been prompted by US 2002/0006933 to administer the drug by inhalation as this route did not offer any advantages over the conventional sublingual route. For example, an increased incidence of emesis was noted when the drug was administered by 'inhalation' compared to sublingual administration (virtually every dog in the study suffered emesis within five minutes of 'inhaling' the drug (see Table 3). Further, the incidence of emesis relative to the amount of drug in the subject's system (measured as AS/C_{max}) was thus much higher for 'inhalation' than it was for intranasal therapy (see Table 4). Accordingly, Applicants submit that US 2002/0006933 teaches away from inhalation therapy.

Instead, Applicants submit that the skilled person would have been motivated by US 2002/0006933 to administer apomorphine intranasally because the bioavailability was greatly improved in comparison to that achieved by sublingual administration (see Table 2) or orally because the incidence of emesis was greatly reduced (see Table 5). In fact, Applicants submit that, there is nothing in US 2002/0006933 that would have prompted the skilled person to further look to inhalation methods, which offered no advantages over the conventional sublingual route at all. Applicants, therefore, submit that the skilled person would not have looked to the other documents cited by the Examiner, as they are directed to administration by inhalation, something that US 2002/0006933 teaches away from.

Further, Applicants submit that, even if the skilled person had consulted these secondary documents (a position which is refuted), they would not have helped solve the deficiencies of US 2002/0006933 because they offer no guidance as to the specific human inhalation dose of active agent that would be appropriate. Applicants submit that none of the cited documents (i.e., US 5,699,789, Ensuring Patient Care, US 5,476,093 Lucas P. *et al.* or Noakes T.J.) teach or suggest that a human inhalation dose "of from about 100 to about 1600 micrograms of

apomorphine or a pharmaceutically acceptable salt or ester thereof," as recited in claims 1 and 34.

For the foregoing reasons, Applicants submit that the subject matter of amended claims 1 and 34 and the claims dependent therefrom is not rendered obvious by the combination of the cited documents.

With regard to amended independent claim 22, Applicants submit that the combination of the cited documents does not teach or suggest a method for treating sexual dysfunction, comprising: inhaling a dose including apomorphine or a pharmaceutically acceptable salt or ester thereof, "said dose being sufficient to provide a therapeutic effect in about nine minutes or less." In support of this position, the Examiner's attention is directed to Example 2 of US 2002/0006933. Applicants submit that for each apomorphine dose investigated in the study of Example 2 of US 2002/0006933, C_{max} was only reached after about 10 minutes (Table 4) after intranasal administration, while oral ingestion enabled C_{max} to be achieved after about 8 minutes (Table 6). Applicants further submit that only pharmacokinetic parameters were measured in the studies described in US 2002/0006933; and that no pharmacodynamic data were presented or even commented upon. Accordingly, Applicants submit that the combination of the cited documents does not teach or suggest that inhalation as a route of administration enables a therapeutic effect to be achieved any quicker than by any other route of administration. Therefore, Applicants submit that the combination of the cited documents does not teach or suggest a dose "being sufficient to provide a therapeutic effect in about nine minutes or less" as recited in amended independent claim 22.

Applicants respectfully notes that the Examiner is failing to compare like with like when alleging that the subject matter of amended claim 22 is obvious in light of US 2002/0006933, for example, because, in Example 2 of US 2002/0006933, apomorphine is administered as a solution directly into the trachea, whereas, in the method of the present claims, the formulations are inhaled, e.g., as a dry powder formulation.

Accordingly, Applicants submit that there is nothing in US 2002/0006933 (or any of the other documents relied upon by the Examiner) to suggest that inhalation of apomorphine could achieve "a therapeutic effect in about nine minutes or less" as recited in amended claim 22.

Therefore, Applicants submit that the combination of the cited documents would not motivate the skilled person to investigate inhalation as a route of administration any further, let alone to prepare formulations comprising apomorphine for inhalation that enable a therapeutic effect to be achieved in nine minutes or less as recited in claim 22. Rather, Applicants submit that the cited documents, as a whole, would discourage the skilled person from investigating inhalation as a route of administration, and instead, would motivate the skilled person to further investigate intranasal administration or oral ingestion, as the combination of documents teaches advantages of intranasal and oral ingestion over both conventional sublingual therapy and the 'inhalation' of apomorphine, e.g., as described in US 2002/0006933.

For the foregoing reasons, Applicants submit that the combination of the cited documents does not render the present claims obvious, and respectfully request withdrawal of the obviousness rejection.

CONCLUSION

Reconsideration of the present application, as amended, is requested. If, upon review, the Examiner is unable to issue an immediate Notice of Allowance, the Examiner is respectfully requested to telephone Applicant's undersigned attorney in order to resolve any outstanding issues and advance the prosecution of the case.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,
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